Original Article

Successful Outpatient Graded Administration of Trimethoprim-Sulfamethoxazole in Patients Without HIV and With a History of Sulfonamide Adverse Drug Reaction

Regan C. Pyle, DO[a], Joseph H. Butterfield, MD[a], Gerald W. Volcheck, MD[a], Jenna C. Podjasek, MD[a], Matthew A. Rank, MD[b], James T.C. Li, MD, PhD[a], Amitha Harish, MD[c], Kimberly L. Poe, RN[a], and Miguel A. Park, MD[a]

Rochester, Minn; Scottsdale, Ariz; and Portsmouth, NH

What is already known about this topic? Trimethoprim-sulfamethoxazole desensitization in patients with a history of sulfonamide adverse drug reaction is safe and effective in patients with HIV but unknown in the patients without HIV.

What does this article add to our knowledge? Trimethoprim-sulfamethoxazole desensitization in patients without HIV and with a history of sulfonamide adverse drug reaction is safe and effective in patients without HIV.

How does this study impact current management guidelines? Clinicians will be able to better quantify and discuss the risks and benefits of trimethoprim-sulfamethoxazole desensitization in patients without HIV.

BACKGROUND: The outcomes of trimethoprim-sulfamethoxazole (TMP-SMX) desensitization have been widely reported in the HIV literature but less so in the non-HIV literature.

OBJECTIVE: To evaluate the safety and efficacy of graded administration of TMP-SMX in patients without HIV and with a history of TMP-SMX adverse drug reaction (ADR).

METHODS: A retrospective chart review, 2004-2012, of all the patients without HIV seen in the Division of Allergic Diseases and with a history of TMP-SMX ADR who underwent outpatient graded administration of TMP-SMX was conducted. The medical record was reviewed for age, sex, details of the initial ADR to TMP-SMX, an indication for TMP-SMX administration, and outcome. Patients also were contacted by telephone, and medical records were reviewed to determine long-term outcomes.

RESULTS: Seventy-two patients (46 women [64%]; mean [SD] age, 57.7 ± 13.89 years]) were included. The most common patient-reported reactions to TMP-SMX were rash 39 (54%), and hives 9 (13%). TMP-SMX administration was needed for the following indications: prophylaxis (62 [86%]) and treatment of infection (10 [14%]). Forty-three of the patients (60%) underwent a 1-day TMP-SMX administration protocol. Thirty-five of the 43 (81%) underwent a 6-step (90 minutes to 6 hours) protocol and 7 of the 43 (16%) underwent a novel 14-step TMP-SMX protocol. Twenty-nine (40%) underwent a >1-day TMP-SMX administration protocol. Our overall success rate was 90% (mean duration of 11 months). Ninety-eight percent of the patients successfully completed a 1-day graded administration protocol, and 76% successfully completed a >1-day protocol. TMP-SMX was stopped in 8 patients because of the ADR.

CONCLUSION: We report the largest case series of successful outpatient graded administration of TMP-SMX with both 1-day and >1-day protocols, which have shown to be safe and well tolerated in patients without HIV and with a history of sulfonamide ADR. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014; 2:52-8)

Key words: *Adverse drug reaction; Drug hypersensitivity; Drug intolerance; Immunologic; Graded challenge; Trimethoprim-sulfamethoxazole*

Trimethoprim-sulfamethoxazole (TMP-SMX) is highly effective and is the first-line agent for methicillin-resistant *Staphylococcus aureus*. It also is the first-line agent for *Pneumocystis carinii* pneumonia (PCP) prophylaxis in patients with immunosuppression associated with cancer,[1] transplant, and rheumatologic diseases. Alternative PCP treatments, including atovaquone and pentamidine are less efficacious[2] and less cost effective[3] compared with TMP-SMX. Moreover, the recent shortage of pentamidine[4] further supports the use of TMP-SMX for PCP prophylaxis and treatment of infections.

TMP-SMX is a widely prescribed antibiotic and a common cause of adverse drug reactions (ADR). In hospitalized patients from June

[a]Division of Allergic Diseases, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, Minn

[b]Division of Allergy, Asthma, and Clinical Immunology, Mayo Clinic, Scottsdale, Ariz

[c]Allergy Associates of New Hampshire, Portsmouth, NH

No funding was received for this work.

Conflicts of interest: J. H. Butterfield has received royalties for the HMC-1 cell line from MedImmune; Amgen; Janssen Biotech; Wyeth-Ayerst Research division of Wyeth-Ayerst Pharmaceuticals; Actelion Pharmaceuticals; Becton, Dickinson and Company; and Blueprint Medicines Corporation. J. T. C. Li has stock/stock options in Novartis and Abbott. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication June 5, 2013; revised October 22, 2013; accepted for publication November 1, 2013.

Corresponding author: Miguel A. Park, MD, Division of Allergic Diseases, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. E-mail: park.miguel@mayo.edu.

2213-2198/$36.00

http://dx.doi.org/10.1016/j.jaip.2013.11.002

Abbreviations used
ADR- Adverse drug reaction
PCP- Pneumocystis carinii pneumonia
PO- Orally
TMP-SMX- Trimethoprim-sulfamethoxazole

1975 to June 1982, TMP-SMX was the second most common medication that caused a cutaneous ADR (33.8 reactions per 1000 patients exposed) behind amoxicillin (51.4/1000).[5] More recently, Macy and Poon[6] reported antibiotic allergy incidence in the outpatient setting was highest for sulfas in both male and female patients compared with other classes of antibiotics. TMP-SMX use has been associated with cutaneous reactions, morbilliform rash with fever and systemic symptoms, immediate-type hypersensitivity reactions (hives, angioedema, and anaphylaxis), Steven-Johnson syndrome, toxic epidermal necrolysis, and serum sickness.[7]

The term desensitization has traditionally been used for IgE-mediated ADR. Although the mechanism of most TMP-SMX hypersensitivity reactions is unlikely IgE-mediated,[7] the term desensitization has been used to describe the various protocols to induce tolerance to TMP-SMX after an ADR. Successful TMP-SMX desensitization in patients with HIV by using both 1-day and >1-day protocols has been widely reported in the literature.[8-29] In patients with HIV and with a history of TMP-SMX ADR, most patients (54%-100%)[8-29] have been able to tolerate TMP-SMX safely when desensitized. However, there is very little information regarding the outcomes of graded administration of TMP-SMX in patients without HIV and with a history of TMP-SMX ADR.[30-34] In this study, we show that outpatient graded administration with escalating doses of either 1-day or >1-day TMP-SMX protocols in patients without HIV and with a history of TMP-SMX ADR is feasible and safe, which is the largest case series reported. In addition, we introduce 2 novel 1-day TMP-SMX administration protocols: the flexible-interval 6-step and the 14-step schedules.

METHODS

Subjects

The 72 consecutive patients without HIV and with a history of TMP-SMX ADR referred to the Division of Allergic Diseases who underwent a TMP-SMX graded administration from 2004-2012 constitute the patient population. The patients were not offered graded administration if they had a history of Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms, serum sickness, or other severe delayed hypersensitivity reactions. The Mayo Clinic Institutional Review Board approved the study, and all subjects signed a written informed consent.

Study design

Medical records were reviewed for basic demographics (age and sex), patient-reported symptoms associated with TMP-SMX use, the indication for readministration of TMP-SMX, the TMP-SMX graded administration protocol used (Tables I to III), the initial completion rate of TMP-SMX administration, and adverse outcomes from the TMP-SMX administration, short-term (within 24 hours of the time frame of the protocol) and long-term (>24 hours after the completion of the protocol) completion of TMP-SMX therapy (either for prophylaxis or treatment) was evaluated approximately 2 months after the end date of the study time frame by both telephone and chart review. The patients were asked how long they took TMP-SMX, what (if any) adverse reaction was experienced, and if this prompted discontinuation of TMP-SMX. A significant ADR included potentially life-threatening anaphylaxis with

TABLE I. TMP-SMX graded administration protocols: TMP-SMX 6 step (1 day)*†

Step	Dose of TMP/SMX, mg/mg
1	0.02/0.004
2	0.2/0.04
3	2/0.4
4	20/4
5	200/40
6	Final dose: single, 400/80 PO, or double, 800/160 mg PO

PO, orally.
*Dosing intervals are flexible and could be scheduled at 15, 30, or 60 min apart.
†Modified from the desensitization protocol by Gluckstein and Ruskin.[12]

TABLE II. TMP-SMX graded administration protocols: TMP-SMX 14 step (1 day)*†

Step	Dose of TMP/SMX, mg/mg
1	0.08/0.016
2	0.16/0.032
3	0.32/0.064
4	0.64/0.128
5	1.28/0.256
6	2.5/0.512
7	5/1
8	10/2
9	20/4
10	40/8
11	80/16
12	160/32
13	320/64
14	440/88

*Dosing interval is 15 minutes apart.
†A shorter version of our 20-step TMP-SMX desensitization inpatient protocol. Modified from the desensitization protocol outlined by Kalanadhabhatta et al.[13]

TABLE III. TMP-SMX graded administration protocols: TMP-SMX 10 step (>1 day)*†

Step	Dose of TMP/SMX, mg/mg
1	2/0.4
2	4/0.8
3	8/1.6
4	16/3.2
5	40/8
6	80/16
7	160/32
8	320/64
9	400/80
10	800/160

*Dosing interval is daily.
†Reprinted from reference 9.

TABLE IV. Characteristics of patients undergoing TMP-SMX graded administration

	No. (%)
Total no. of patients (average [SD)] age, 57.7 ± 13.89 y)	72 (100)
Sex	
Women	46 (64)
Men	26 (36)
Patient-reported symptoms with TMP-SMX	
Rash	39 (54)
Hives	9 (13)
Unknown	6 (8)
Itching	5 (7)
Nausea and/or vomiting	3 (4)
Flushing	4 (5)
Swelling	3 (4)
Malaise	3 (4)
Indication for TMP-SMX administration	
PCP prophylaxis	62 (86)
Solid organ transplantation	18 (25)
Hematologic transplantation	17 (24)
Hematologic malignancy, on immunosuppression	11 (15)
Rheumatologic disease, on immunosuppression	10 (14)
Immunodeficiency (common variable immunodeficiency)	2 (3)
Bronchial stenosis, immunosuppression	1 (1)
Interstitial pneumonitis, on immunosuppression	1 (1)
Cryptogenic organizing pneumonia, on immunosuppression	1 (1)
Abeta-associated angiitis, on immunosuppression	1 (1)
Treatment of infection	10 (14)
Pulmonary nocardiosis	4 (6)
Bone/soft tissue infection	3 (4)
Recurrent urinary tract infection	2 (3)
Pulmonary *Mycobacterium avium* complex	1 (1)
Administration protocol	
1-Day protocols	
6 step	36 (50)
14 step	7 (10)
>1-Day protocol	
10 step	29 (40)

TABLE V. ADRs in patients who underwent 1-day TMP-SMX administration protocols (n = 43)

Patient no.	Symptom	Time to reported ADR (min)	Stopped treatment
1	Facial flushing	40 (step 5)	No
2	Headache	105 (step 7)	No
3	Headache, itching	360	No
4	Itching	90	No
5	Flushing, nausea	60, 390	No
6	Itching	50	No
7	Rash and lip swelling	360	Yes

hypotension, Stevens Johnson syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms or the physician stopped the administration due to his or her clinical judgment.

Patients underwent either 1-day (6 step or 14 step) or >1-day (10 day [10 step]) TMP-SMX administration protocols at the discretion of the allergist evaluating and treating the patient. The 6-step protocol, a flexible-interval schedule (90 minutes to 6 hours), was modified from the desensitization protocol by Gluckstein and Ruskin.[12] The novel 14-step schedule, a shorter version of our 20-step TMP-SMX inpatient graded administration protocol, was modified from the desensitization protocol outlined by Kalanadhabhatta et al.[13] The 10-step protocol was modified from the desensitization protocol by Absar et al.[9] There were no set criteria or protocol that determined which schedule was chosen. Our primary outcome was to assess the completion rates and safety of these schedules in patients without HIV. By using the Fisher exact test, we compared the differences in the proportion of failure rates (short term and long term) between patients who underwent the 1-day TMP-SMX administration protocols compared with patients who underwent the >1-day TMP-SMX administration protocols. A P value <.05 was considered statistically significant.

RESULTS

The baseline demographic and clinical characteristics of the 72 patients are noted in Table IV. The majority of the patients were women (64%), with rash (54%) being the most common patient-reported symptom experienced. All the patients had an indication for taking TMP-SMX with PCP prophylaxis (86%) due to solid organ (25%) or hematologic transplantation (24%) being the most common, followed by treatment of infection (14%). Thirty-six (50%) underwent the 6-step (15 minutes [n = 15], 30 minutes [n = 15], 60 minutes [n = 6]), and 7 (10%) underwent the 14-step TMP-SMX administration protocols. Twenty-nine (40%) of the patients underwent the 10-step TMP-SMX schedule in >1 day.

ADRs of patients who underwent 1-day TMP-SMX administration protocols (n = 43) are reported in Table V. Seven of the 43 patients (16%) developed symptoms, with a mean onset of 178 minutes. Patient no. 5 reported 2 symptoms at separate times during the administration. All the patients were able to complete the graded administration despite the ADR, except for patient no. 7 who developed rash and lip swelling after 360 minutes. The overall ADR rate for those undergoing 1-day TMP-SMX administration protocols was 16%, with an overall failure rate of 2%.

ADRs of patients who underwent >1-day TMP-SMX protocols (n = 29) are reported in Table VI. Eighteen of the 29 patients (62%) developed symptoms, with a mean onset of 36 days. Eight of the 18 patients (44%) discontinued the TMP-SMX because of the ADR. Five of the 18 patients (17%) stopped their administration before completion because of the ADR, with a mean ADR onset of 7 days. Patient no. 24 developed flushing, nausea, and vomiting from the end of the administration until 28 days later, which prompted discontinuation of TMP-SMX, however, despite discontinuing the medication, the patient's symptoms remained unchanged. Patient no. 26 developed diarrhea on day 1 and discontinued TMP-SMX but was able to restart it at the full dose 2 weeks later and tolerated it well without any further ADR (this patient was excluded from the overall failure rate). Four patients (including patient no. 24) developed ADRs after completing the administration, with a mean onset

TABLE VI. ADRs in patients who underwent >1-day TMP-SMX administration protocols (n = 29)

Patient no.	Symptom	Time to reported ADR, d	Stopped treatment
8	Itching	8	No
9	Itching	3	No
10	Itching	3	No
11	Itching, redness at base of neck	2 and 7	No
12	Nausea	3	No
13	Rash, itching	3	No
14	Dizzy	3	No
15	Rash	Present before administration but worsened day 9	No
16	Rash	119	No
17	Itchy rash	10	No
18	Baseline itching made worse	6	Yes
19	Drug reaction vs graft-versus-host disease	10	Yes
20	Increased creatinine	3	Yes
21	Low blood counts	196	Yes
22	Increased international normalized ratio	30	Yes
23	Flushing, nausea, and vomiting	From end of graded administration to 28 d	Yes, but still had the same symptoms when off TMP-SMX
24	Increased creatinine	30	Yes
25	Diarrhea	1	Yes, but restarted 2 wk later and tolerated treatment well without ADR

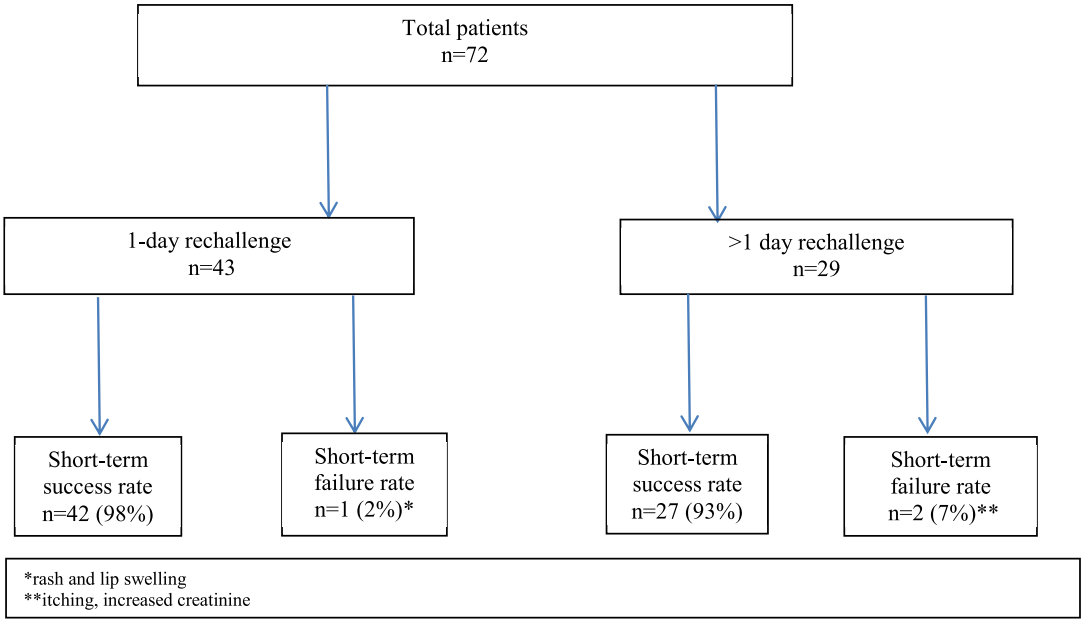

FIGURE 1. Short-term (within 24 h of the time frame of the protocol) outcomes of the study.

of 25 days. The overall ADR rate for those undergoing >1-day TMP-SMX protocols was 62%, with an overall failure rate of 24%.

Our study outcomes are reported in Figures 1 and 2. Of the 43 patients who underwent 1-day graded administration protocols, short- and long-term success rates were 98% and 98%, respectively, with an overall failure rate of 5% (mean follow-up of 11 months). Of the 29 patients who underwent >1-day graded administration protocols, short- and long-term success rates were 93% and 81%, respectively, with an overall failure rate of 24% (mean follow-up of 11 months). In summary, 64 of the 72 patients (89%) were able to tolerate the graded administration and treatment and/or prophylaxis regimen, which was carried out for a mean of 11 months. There was a statistical difference between the failure rates of the 1-day and >1-day protocols ($P = .0308$); however, there was no difference in the short-term outcomes ($P = .5609$) as determined by the Fisher exact test.

DISCUSSION

We report the largest case series of successful (89%) TMP-SMX graded administration in patients without HIV. Our study

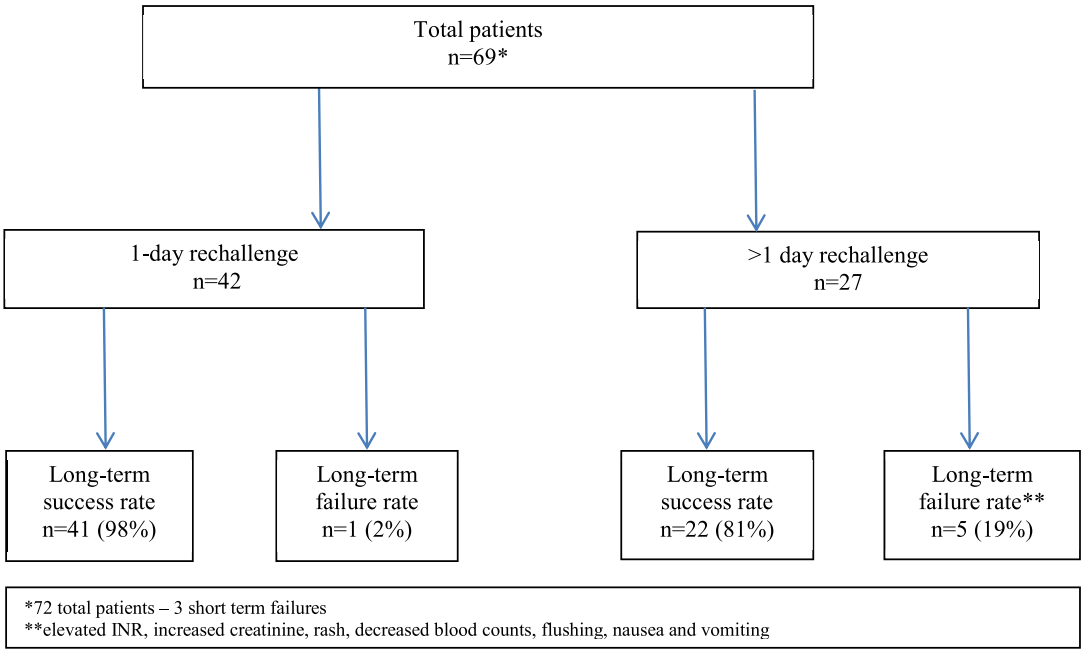

FIGURE 2. Long-term (>24 h after the completion of the protocol) outcomes of the study.

shows that patients with a history of non–life-threatening ADR to TMP-SMX can undergo outpatient graded administration of TMP-SMX safely. Moreover, clinicians will be able to better quantify and discuss the risks and benefits of TMP-SMX graded administration in patients without HIV. Furthermore, we report 2 novel outpatient 1-day TMP-SMX administration protocols: the flexible-interval 6-step and the 14-step protocols (adapted from our 20-step inpatient protocol) give clinicians more options.

Very few studies have been devoted to examining the role of graded administration of TMP-SMX in patients without HIV and with TMP-SMX hypersensitivity.[30-34] Hughes et al[30] reported 2 patients with bone marrow transplantation and with a history of TMP-SMX ADR who successfully underwent a 5-hour TMP-SMX desensitization protocol. Mann et al[31] described 4 patients with a history of TMP-SMX hypersensitivity (leukopenia, hives, macular rash, morbilliform rash) who needed TMP-SMX for prophylaxis against *Pneumocystis* pneumonia. Two of the patients underwent an 8-day protocol, and the remaining 2 underwent a 22-day protocol.[22] None of the 4 patients developed a reaction to TMP-SMX. Soffritti et al[32] reported a 7-year-old boy with a history of hematopoietic stem cell transplantation and TMP-SMX hypersensitivity who underwent a successful 16-day TMP-SMX desensitization. Patriarca et al[33] described an 85-year-old woman with a history of fixed drug eruption from cotrimoxazole who successfully completed a 4-day desensitization protocol (observed for 10 days) to treat a staph infection. Nucera et al[34] reported a 44-year-old pregnant woman with toxoplasmosis who successfully underwent a 4-day cotrimoxazole protocol. Our larger study is consistent with the 9 patients without HIV who successfully underwent TMP-SMX graded administration described in the literature[30-34] with regard to short-term success rates in both the 1-day and >1-day protocols. Longer-term data could not be compared because it was not reported in the non-HIV studies.

There are a few studies that evaluated 1-day TMP-SMX protocols in the HIV patient population with overall success rates that ranged from 60% to 100%.[12,13,20] Gluckstein and Ruskin[12] reported 19 patients who successfully completed 5-hour desensitization protocols (86% short-term success rate), with a long-term success rate of 71% and who took TMP-SMX for a mean of 14 months. Kalandhabhatta et al[13] reported a 100% success rate of 13 patients with HIV who underwent TMP-SMX desensitization over a 24-hour period, and, long term, none of the patients developed adverse reactions to TMP-SMX during the 4- to 84-week follow-up period. Moreno et al[20] reported that 11 of 13 patients (85%) were successfully desensitized to sulfonamides by using both rapid (2.5 hours) and slow (5-6 days) methods. Our larger study showed a similar success rate (98%) for those undergoing 1-day protocols with comparable failure rate (2%) than that reported in the HIV literature with similar follow-up times. Interestingly, the results from our >1-day TMP-SMX administration protocols are most similar to the HIV studies with patients undergoing >1-day protocols with regard to both short-term (90% vs 42%-100%)[8,9,15,21,24,26,28,29] and long-term (85% vs 54%-100%)[8,9,27,28] success rates, overall success rates (76% vs 54%-97% follow-up from 5 days to 23 months),[8-29] and the ADR rate (35% vs 13%-47%).

The high success rate of TMP-SMX graded administration in our patients without HIV is similar to the patients with HIV and with a history of TMP-SMX hypersensitivity (90% compared with 42%-100%,[8-29] respectively). Moreover, as with the patients without HIV, the different schedules used in patients with HIV varied greatly but still had similar success rates.[8-29] When patients with HIV and with a history of TMP-SMX hypersensitivity were randomized to graded or to full-dose administration, they showed similar success rates in tolerating TMP-SMX. Bonfanti et al[10] showed 79.5% of 34 patients positive for HIV who underwent graded administration versus 72% of 25 patients who underwent full-dose administration

successfully tolerated TMP-SMX. Similarly, Straatmann et al[18] revealed that 60% of patients with AIDS successfully underwent oral desensitization with escalating doses versus 60% with full-dose administration. When comparing full-dose administration success rates (58%-72%)[10,14,18] versus the long-term success rates of the graded administration (60%-80%),[10,14,18] they appear very similar. However, Leoung et al[14] showed a higher success rate among the dose-escalation group (75%) versus the full-dose administration group (58%) ($P = .014$) in patients positive for HIV. Patients with moderate-to-severe ADR to TMP-SMX were excluded from these studies, hence, they may not be generalizable to patients with more severe TMP-SMX hypersensitivity HIV. In our study, the majority of the patients underwent a short 6-step protocol (Table I).

There are a few limitations to our study. First, both 1-day and >1-day TMP-SMX administration protocols were used, and the majority of the patients without HIV and with mild ADR to TMP-SMX may have selectively undergone the 1-day protocol. Caution may be indicated in patients with a more-severe history of ADR to TMP-SMX if the 1-day TMP-SMX administration protocols are to be used. Second, the rates of successful TMP-SMX administration may be falsely high because only the clinical history was used to determine the clinical likelihood of a true, reproducible, immunologically mediated TMP-SMX ADR. In penicillin allergy, a clinical history has been an unreliable means of determining the clinical likelihood of a true penicillin allergy.[35,36] However, in published studies, most of the HIV and non-HIV TMP-SMX desensitizations also used the clinical history to determine the clinical likelihood of a true, reproducible, immunologically mediated TMP-SMX ADR.[6-34,37-40] Third, the study was conducted in a tertiary care center, which may limit the generalizability of the study.

CONCLUSION

To our knowledge, we report the largest case series ever of successful outpatient TMP-SMX graded administration in patients without HIV and with a history of TMP-SMX ADR. In addition, we are the first to report 2 novel 1-day outpatient TMP-SMX graded administration protocols: the flexible-interval 6-step and the 14-step protocols.

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